INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001911

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C12N 15/11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL,WPI,PAJ,BIOSIS,MEDLINE,EMBASE,CHEM.ABS.DATA,REGISTRY,EBI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03070970 A2 (RIBOZYME PHARMACEUTICALS,INC.), 28 August 2003 (28.08.2003), page 12, line 8 - page 14, line 5; page 19, line 2 - page 23, line 20; page 28, line 17 - page 30, line 12; page 32,line 5-page 33, line 18, tables 2 & 3, claims --	1-31
X	WO 03070918 A2 (RIBOZYME PHARMACEUTICALS, INCORPORATED), 28 August 2003 (28.08.2003), page 135 --	1-31

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2005	11 -04- 2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Terese Persson /itw Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"RNA INTERFERENCE DIRECTED AGAINST VIRAL AND CELLULAR TARGETS INHIBITS HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 REPLICATION." Rama M.Surabhi et al In:Journal of Virogoly;Dec 2002,p.12964,column 1, paragraph 5 --	1-31
X	"Identification of NF-kB-regulated genes induced by TNF alfa utilizing expression profiling and RNA interference." page 2062,column 1,paragraph 2 --	1-31
X	§ 2289,JEREMIAH SAVAGE et al "Cellular,Molecular and Tumor Biology." In:Proceedings of America Association for Canser Research,vol. 44,2nd ed,July 2003 --	1-31
X	WO 03020754 A2 (UNIVERSITY COURT OF THE UNIVERSITY OF DUNDEE), 13 March 2003 (13.03.2003), page 32 - page 33 --	1-31
P,X	REGULATION OF MONOCYTE CHEMOATTRACANT PROTEIN-1 BY THE OXIDIZED LIPID,13-HYDROPEROXYOCTADECADIENOIC ACID,IN VASCULAR SMOOTH MUSCLE CELLS VIA NUCLEAR FACTOR-KAPPA B (NF-kB).R.S.DWARAKANATH et al. tables 1 & 2:page 587,column 1,paragraph 3 In:Journal of Molecular and Cellular Cardiology --	1-31

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28-31
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 28-31 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv).

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

.../...

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box II/III

II.1
Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the siRNA molecules.

III
The following separate inventions were identified:

1) Claims 1-5 (partly), 6 and 9-31 (partly)
A siRNA molecule which down regulates expression of a p65 subunit of NF-kappa-B gene comprising a sense and an antisense region wherein said antisense region comprises the sequence SEQ. ID. NO. 5 or a substantially homologous sequence thereof. Applications thereof.

2) Claims 1-5 (partly), 7 and 9-31 (partly)
A siRNA molecule which down regulates expression of a p65 subunit of NF-kappa-B gene comprising a sense and an antisense region wherein said antisense region comprises the sequence SEQ. ID. NO. 6 or a substantially homologous sequence thereof. Applications thereof.

3) Claims 1-5 (partly), 8 and 9-31 (partly)
A siRNA molecule which down regulates expression of a p65 subunit of NF-kappa-B gene comprising a sense and an antisense region wherein said antisense region comprises the sequence SEQ. ID. NO. 8 or a substantially homologous sequence thereof. Applications thereof.

It was considered that all inventions could be searched within one fee. Therefore, no additional fees are required.

The present application has been considered to contain 3 inventions which are not linked such that they form a single general inventive concept, as required by Rule 13 PCT for the following reasons:

Claims 1-31 describe siRNA molecules which down regulate expression of a p65 subunit of NF-kappa-B gene. These siRNA molecules are targeted to different sites within the sequence encoding the p65 subunit. Such siRNA molecules might be used for preventing/treating/alleviating NF-kappa-B dependent conditions such as e.g. cancer.

The closest prior art has been identified as:
D1: WO 03070970 A2

.../...

Box III

D1 discloses a number of different siRNA molecules targeted to the sequence encoding the p65 subunit of the NF-kappa B gene (also called Rel-A). These may be used for treating conditions involving NF-kappa-B, e.g. cancer. One of the siRNA molecules disclosed in D1, the one composed of SEQ. ID. NOs. 11 and 147, fulfils the requirements in claim 1. The antisense region (SEQ. ID. NO. 147) is substantially complementary to SEQ. ID. NO. 2 and is substantially homologous to SEQ. ID. NO. 6. According to the description, two sequences are "substantially homologous" when at least 15 nucleotides match. Between SEQ. ID. NO. 147 in D1 and SEQ. ID. NO. 6 in the present application 17 nucleotides match. SEQ. ID. NO. 2 in the present application correspond to positions 183-203 according to the numbering used in D1. The siRNA molecules composed of SEQ. ID. NOs. 32 and 168; 51 and 187; and 92 and 228 fulfil the requirement that the antisense regions are substantially complementary to SEQ. ID. NOs. 3, 1 respectively 4. However, the sequences of the antisense regions differ. (Abstract; page 12, line 8-page 14, line 15; page 19, line 2-page 23, line 20; page 28, line 17-page 30, line 12; page 32, line 5-page 33,line 18; tables 2 and 3; claims.)

The special technical feature of invention 1 that makes a contribution over this prior art (Rule 13.2 PCT) is the specific sequence SEQ. ID. NO. 5 and substantially homologous sequences thereof. This difference has not been shown to give rise to any unexpected technical effect. From this special technical feature the objective problem to be solved by this and all further inventions is to provide alternative siRNA molecules having the ability to down regulate the expression of a p65 subunit of the NF-kappa-B gene.

A number of different solutions to this problem are provided, comprising alternative siRNA molecules. No common concept or common structural feature which makes a contribution over the prior art has been found linking the different inventions. The above analysis shows that the special technical feature of invention 1 is neither the same or nor corresponding to that of any of the inventions 2-3.

In conclusion, therefore, the inventions are not linked by same or corresponding special technical features and define different inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in Rule 13.1 and 13.2 PCT.

INTERNATIONAL SEARCH REPORT

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